Communication

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Assessing Antibiotic Safety: A Comparative Study of Four Promising Candidates Using pKCSM Database

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Abstract: This study centered on examining 60 different antibiotics by assessing their primary toxicity parameters through the pkCSM database. The parameters included Max. Tolerated Dose (Human) (log mg/kg/day), Oral Rat Acute Toxicity (LD50) (mol/kg), Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day), and Minnow Toxicity (LC50) (log mM). The results highlight four potential antibiotics—cefotaxime, ceftriaxone, imipenem, and meropenem—that exhibited lower toxicity effects compared to other compounds. These findings imply a relatively favorable safety profile for these antibiotics concerning the specified toxicity parameters. However, it is crucial to interpret these outcomes within the context of the specific clinical application and to consider additional factors for a comprehensive safety assessment. It's essential to acknowledge that evaluating toxicity is intricate, and the determination of what is considered "less toxic" can rely on specific criteria and the context of use. Furthermore, individual responses to antibiotics may vary, and the selection of an antibiotic should be based on diverse factors, including the specific infection being treated, the patient's health, and potential side effects.

Keywords: antibiotics; pkCSM; max.tolerated dose (human); oral rat chronic toxicity; oral rat acute toxicity

1. Introduction

Antibiotics are substances employed to address infections stemming from bacterial sources. They exhibit diverse modes of action, including hindering bacterial growth, eradicating bacteria, or impeding their reproductive processes. Within the realm of medicine, antibiotics find extensive use in treating a broad spectrum of bacterial infections[1–4].

It's crucial to recognize that antibiotics lack efficacy against viral infections, such as the common cold or influenza. Inappropriate antibiotic utilization, such as unnecessary intake or failure to complete the prescribed regimen, can contribute to the emergence of antibiotic-resistant bacteria, constituting a burgeoning concern in public health. Antibiotics are categorized based on their mechanism of action and their target bacteria. Examples encompass penicillins, cephalosporins, tetracyclines, macrolides, quinolones, and sulfonamides[1–4].

Antibiotics are generally grouped into classes based on their chemical structure. It is important to note that antibiotics of the same class can affect the body differently and can be effective on different bacteria. Let's review the main antibiotic classes based on their mechanism of action[1,2].

Figure 1 shows the mechanical actions of several antibiotics.

This work present a brief overview of some main antibiotic classes and their general mechanisms of action[5–7]:

-Penicillins:

Mechanism: Inhibit bacterial cell wall synthesis by binding to enzymes (penicillin-binding proteins) involved in cell wall formation.

Example: Amoxicillin, Ampicillin.

-Cephalosporins:

Mechanism: Similar to penicillins, they also target bacterial cell wall synthesis.

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Example: Cephalexin, Ceftriaxone.

-Tetracyclines:

Mechanism: Inhibit bacterial protein synthesis by binding to the bacterial ribosome.

Example: Doxycycline, Tetracycline.

-Macrolides:

Mechanism: Interfere with bacterial protein synthesis by binding to the ribosome.

Example: Azithromycin, Erythromycin.

-Quinolones/Fluoroquinolones:

Mechanism: Inhibit DNA gyrase, an enzyme involved in bacterial DNA replication.

Example: Ciprofloxacin, Levofloxacin.

-Sulfonamides:

Mechanism: Inhibit bacterial folic acid synthesis, a crucial component for DNA and RNA synthesis.

Example: Trimethoprim-Sulfamethoxazole (TMP-SMX).

-Aminoglycosides:

Mechanism: Disrupt bacterial protein synthesis by binding to the bacterial ribosome.

Example: Gentamicin, Amikacin.

-Glycopeptides:

Mechanism: Inhibit bacterial cell wall synthesis.

Example: Vancomycin.

-Oxazolidinones:

Mechanism: Inhibit bacterial protein synthesis.

Example: Linezolid.

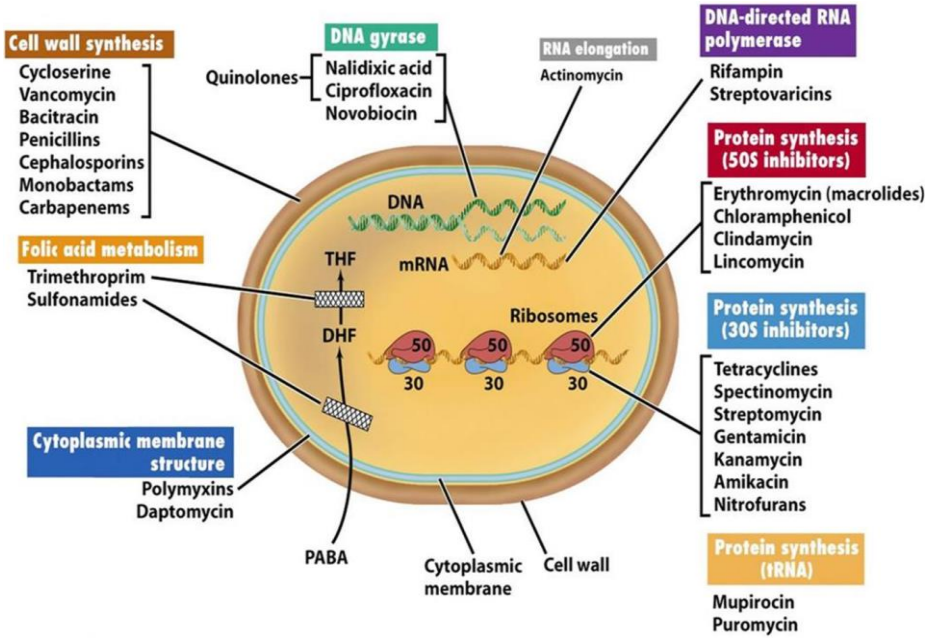

Figure 1. Target sites of antibiotics (Madigan and Martinko, 2006) - "Antibiotics: Classification and mechanisms of action with a focus on molecular perspectives." Figure was reproduced according to Ref [7].

The objective of this succinct scientific investigation is to evaluate different antibiotics based on various parameters related to their mechanisms of action and subsequently use the pkCSM Database[8] to pinpoint the least detrimental among them. several toxicity parameters were performed by PkCSM Database[8] (Preclinical Knowledge-Based Consensus Models) for antibiotics.

These parameters include:

AMES Toxicity: Assessing mutagenicity using the AMES test.

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Max. Tolerated Dose (Human): Determining the maximum dose tolerated by humans.

Oral Rat Acute Toxicity (LD50): Identifying the lethal dose required to cause mortality in 50% of rats after oral administration.

Oral Rat Chronic Toxicity (LOAEL): Establishing the Lowest Observable Adverse Effect Level in rats after prolonged oral exposure.

T. Pyriformis Toxicity: Assessing toxicity specifically related to T. pyriformis (a ciliated protozoan often used in toxicity testing).

Minnow Toxicity: Evaluating toxicity with respect to minnows, a type of small freshwater fish.

These parameters provide a comprehensive view of antibiotic toxicity, encompassing mutagenicity, dose tolerance in humans, acute and chronic effects in rats, as well as specific impacts on aquatic organisms. The use of PkCSM, which relies on these parameters, helps in identifying antibiotics with potentially lower toxicity profiles.

In this communication were investigated of about 60 antibiotics (In Figures 2–5 are reported their chemical structure).

2. Material and Methods

Toxicity parameters thorugh PkCSM [8] investigated are:

-AMES Toxicity>> Positive Test: Indicates that the compound exhibits mutagenic properties

-Oral Rat Acute Toxicity (LD50) [(mol/kg)]>>

-Oral Rat Chronic Toxicity (LOAEL) [(log mg/kg_bw/day)]>>

-T. Pyriformis Toxicity [(log ug/L)]>> T. pyriformis, measured by pIGC50 (the concentration required to inhibit 50% growth), is evaluated for a given compound. If the pIGC50 value is greater than -0.5 log μL/L, it is considered toxic.

-Minnow Toxicity (LC50)[(log mM)]>> LC50 represents the concentration of a molecule required to cause the death of 50% of the population. Furthermore, if the LC50 value is below 0.5 mM (log LC50 < -0.3), it is considered to exhibit high acute toxicity.

-Max. Tolerated Dose (Human)>> [MRTD (log mg/kg/day)]: For a given compound, if the logarithm of the dose in milligrams per kilogram per day is less than or equal to 0.477, it is considered low. If the logarithm of the dose in milligrams per kilogram per day is greater than 0.477, it is considered high.

-Hepatotoxicity

-Skin Sensitisation

3. Results and Discussion

For the first time this work described the toxicity parameters thorugh PkCSM (Preclinical Knowledge-Based Consensus Models) wich it is capable of predicting. PkCSM is a computational tool designed to predict various toxicity endpoints for chemical compounds, including antibiotics[8]. Each of the mentioned toxicity parameters serves a specific purpose in assessing the safety and potential risks associated with the use of antibiotics:

-AMES Toxicity: Predicting mutagenicity through the AMES test helps identify substances that may cause genetic mutations.

-Max. Tolerated Dose (Human): Estimating the maximum dose tolerated by humans assists in understanding the potential for adverse effects at high doses.

-Oral Rat Acute Toxicity (LD50): Predicting the lethal dose in rats after oral administration provides insights into acute toxicity and potential harm.

-Oral Rat Chronic Toxicity (LOAEL): Determining the Lowest Observable Adverse Effect Level in rats after prolonged oral exposure helps assess chronic toxicity.

-T. Pyriformis Toxicity: Assessing toxicity specifically related to T. pyriformis aids in understanding the impact on this organism, often used in toxicity testing.

-Minnow Toxicity: Evaluating toxicity with respect to minnows provides information on the potential harm to small freshwater fish.

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The predictive capabilities of pkCSM in these areas contribute to the early identification of potential risks associated with antibiotics, facilitating more informed decision-making in drug development and safety assessment.

In establishing the relative toxicity of compounds, we must take into account the presented toxicity parameters. These include measures such as AMES toxicity, Max. tolerated dose (human), Oral Rat Acute Toxicity (LD50), Oral Rat Chronic Toxicity (LOAEL), T. Pyriformis toxicity, and Minnow toxicity.It's crucial to emphasize that assessing toxicity requires a thorough analysis, and individual parameters may hold varying degrees of influence on the overall toxicity profile. Furthermore, the criteria for classifying a compound as less toxic may vary based on the specific context and the particular toxicity endpoint under consideration. From these toxicity results, based on the specified parameters: Max. Tolerated Dose (Human) (log mg/kg/day),Oral Rat Acute Toxicity (LD50) (mol/kg), Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day) and Minnow Toxicity (LC50) (log mM)

Four potential antibiotics named cefotaxime,ceftriaxone,imipenem and meropenem respectively are showed lower toxicity compared to other compounds:

- Max. Tolerated Dose (Human) (log mg/kg/day):

cefotaxime: 1,625 log mg/kg/day
ceftriaxone: 1,489 log mg/kg/day
imipenem: 1,431 log mg/kg/day
meropenem: 1.423 log mg/kg/day

-Oral Rat Acute Toxicity (LD50) (mol/kg):

cefotaxime: 2,145 mol/kg
ceftriaxone: 2,352 mol/kg
imipenem: 1,641 mol/kg
meropenem: 1.946 mol/kg

-Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day):

cefotaxime: 2.109 log mg/kg_bw/day
ceftriaxone: 2,269 log mg/kg_bw/day
imipenem: 1.958 log mg/kg_bw/day
meropenem: 2.371 log mg/kg_bw/day

-Minnow Toxicity (LC50) (log mM):

cefotaxime: 4.835 log mM
ceftriaxone: 4,976 log mM
imipenem: 3,435 log mM
meropenem: 4.074 log mM

In each parameter, the values for cefotaxime, ceftriaxone, imipenem, and meropenem are either higher or within a range that indicates lower toxicity compared to other compounds. However, it's essential to consider the specific context and additional factors in a clinical scenario.

To sum Cefotaxime, ceftriaxone, imipenem, and meropenem demonstrated lower toxicity, suggesting a favorable safety profile.

However, clinical application and additional factors must be considered for a comprehensive assessment.

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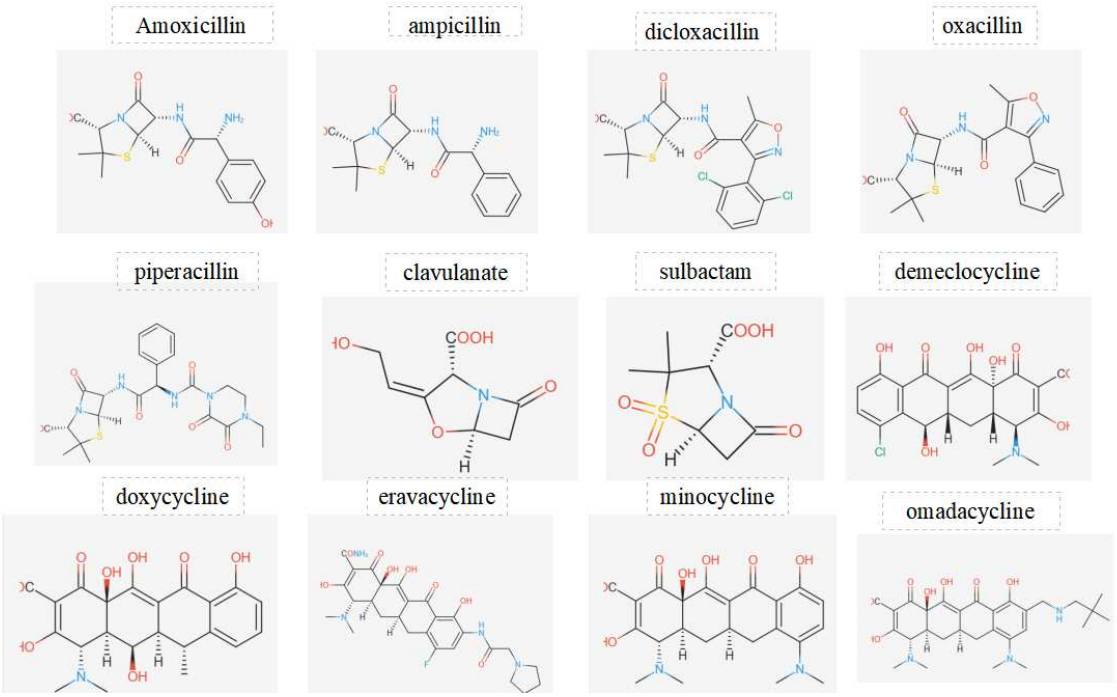

Figure 2. Displays the chemical structures of antibiotics investigated in this work.

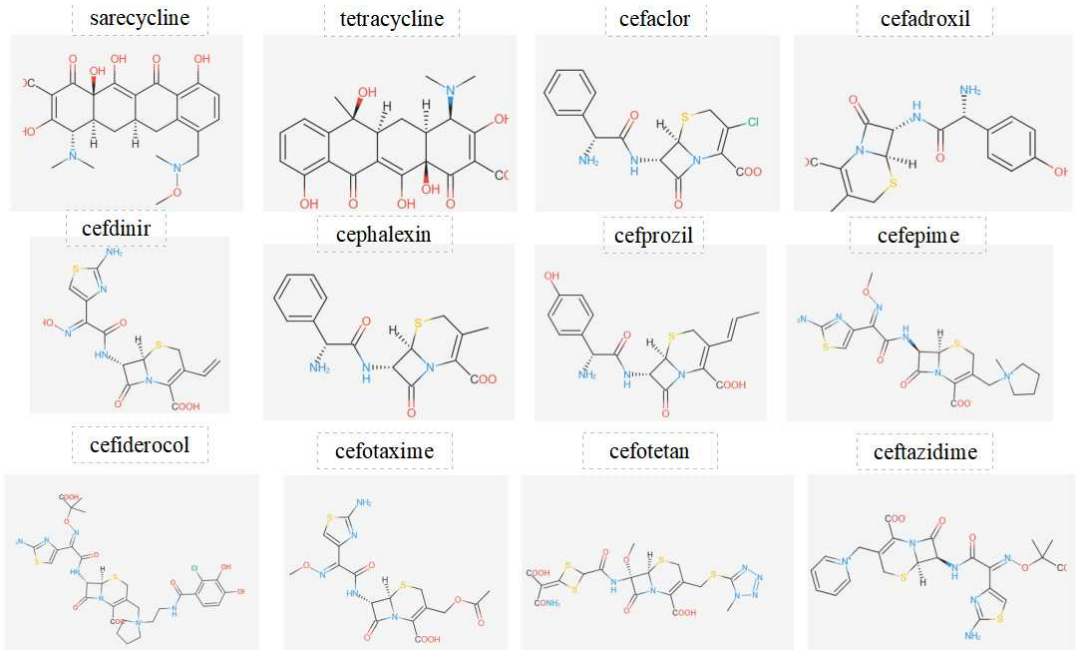

Figure 3. Displays the chemical structures of antibiotics investigated in this work.

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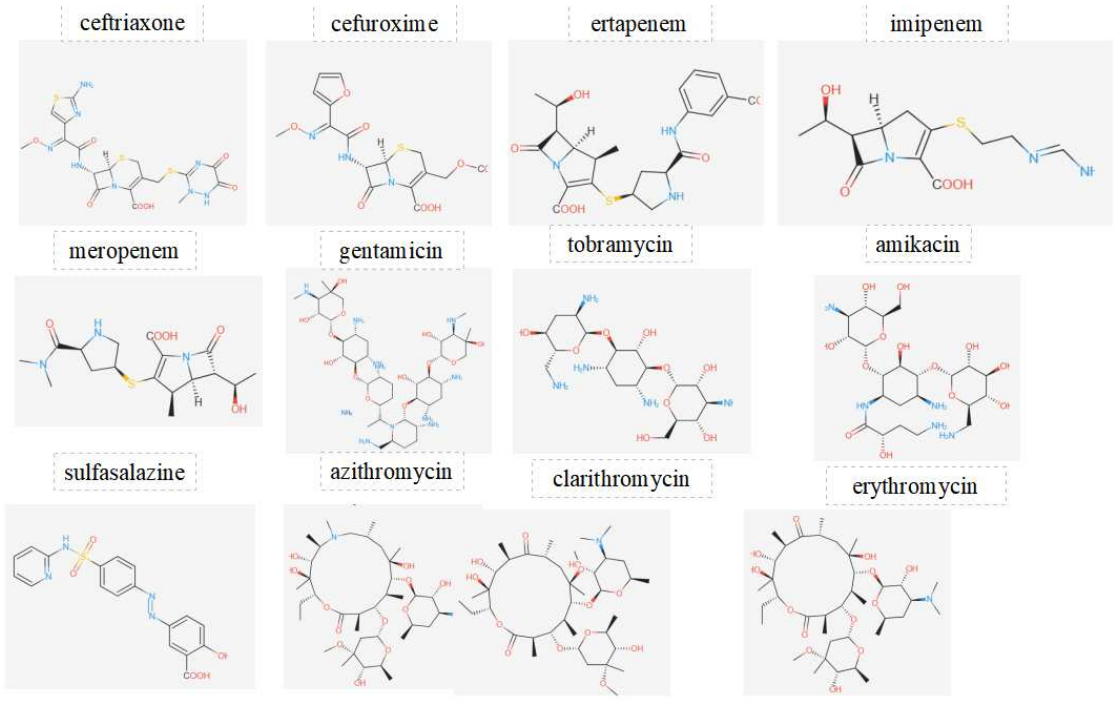

Figure 4. Displays the chemical structures of antibiotics investigated in this work.

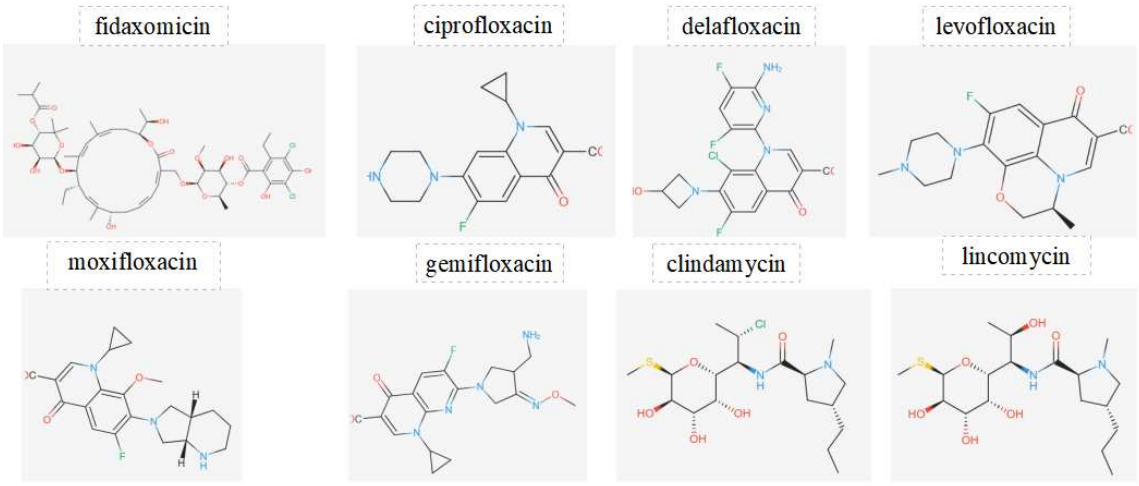

Figure 5. Displays the chemical structures of antibiotics investigated in this work.

Table 1. Displays the comparison of predicted toxicity properties of investigated antibiotics in this work.

Compounds	Brand Name	AMES toxicity	Max. tolerated dose (human) (log mg/kg/day)	Oral Rat Acute Toxicity (LD50) (mol/kg)	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	Hepatotoxicity	Skin Sensitisation	T. Pyriformis toxicity (log ug/L)	Minnow toxicity (log mM)
Amoxicillin	Amoxil	No	1.04	1.77	2.638	yes	no	0.285	4.065

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ampicillin	Unasyn	No	0.921	1.693	2.663	yes	no	0.285	3.502
dicloxacillin	/	No	0.984	2.227	2.404	yes	no	0.285	2.842
oxacillin	/	No	0.67	2.062	2.525	yes	no	0.285	3.286
Phenoxymethylpenicillin	Pen VK	No	0.751	2.037	2.81	yes	no	0.285	3.884
piperacillin	Pipracil	No	0.96	2.149	2.81	yes	no	0.285	5.136
Clavulanic acid	Aumetin	No	1.534	1.441	2.167	yes	no	0.273	3.766
Sulbactam	Unasyn	No	1.234	1.851	2.253	yes	no	0.272	3.689
Demeclocycline	/	No	1.05	2.555	4.427	no	no	0.285	4.601
Doxycycline	Acticlate	No	1.108	2.401	5.056	No	No	0.285	3.518
Eravacycline	Xerava	No	1.19	2.366	4.509	No	No	0.285	4.997
minocycline	Amzeeq	No	0.746	2.235	4.045	No	No	0.285	2.615
omadacycline	Nuzyra	No	0.813	2.392	4.015	No	No	0.285	1.995
sarecycline	/	No	0.843	2.238	4.055	No	No	0.285	2.992
tetracycline	Pylera	No	1.173	2.503	4.288	No	No	0.285	4.775
cefaclor	/	No	0.928	1.836	2.643	yes	No	0.285	3.323
cefadroxil	/	No	1.043	1.771	2.633	yes	No	0.285	4.061
cefdinir	Omnicef	No	1.671	2.244	2.342	yes	No	0.285	3.924
cephalexin	Keflex	No	0.926	1.695	2.658	yes	No	0.285	3.498
cefprozil	/	No	0.903	1.836	2.665	yes	No	0.285	3.739
cefepime	/	No	0.764	1.743	1.448	yes	No	0.285	3.332
cefiderocol	Fetroja	No	1.407	2.403	1.847	yes	No	0.285	3.459
cefotaxime	**Claforan**	**No**	**1.625**	**2.145**	**2.109**	**yes**	**No**	**0.285**	**4.835**
cefotetan	Cefotan	No	1.285	2.378	2.975	yes	No	0.285	3.586
ceftazidime	Avycaz	No	1.365	2.328	1.275	yes	No	0.285	3.054
ceftriaxone	**Rocephin**	**No**	**1.489**	**2.352**	**2.269**	**yes**	**No**	**0.285**	**4.976**
cefuroxime	Ceftin	No	1.264	1.602	2.516	yes	No	0.285	4.397
ertapenem	Invanz	No	0.967	2.209	2.721	yes	No	0.285	3.681
imipenem	**Primaxin**	**No**	**1.431**	**1.641**	**1.958**	**yes**	**No**	**0.285**	**3.435**
meropenem	**Vabomere**	**No**	**1.423**	**1.946**	**2.371**	**yes**	**No**	**0.285**	**4.074**
gentamicin	Gentak	No	0.45	2.482	7.124	No	No	0.285	11.971
tobramycin	Bethkis	No	1.291	1.877	4.144	No	No	0.285	7.987
Amikacin	Arikayce	No	1.11	2.663	5.724	No	No	0.285	11.087
sulfasalazine	Azulfidine	No	0.271	1.682	0.991	No	No	0.305	1.228
azithromycin	Azasite	No	1.252	2.446	1.975	yes	No	0.285	6.118
clarithromycin	Biaxin	No	1.268	2.703	1.658	yes	No	0.285	7.403

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erythromycin	Aktipak	No	1.187	2.517	1.978	yes	No	0.285	6.92
fidaxomicin	Dificid	No	-0.507	3.465	3.382	yes	No	0.285	2.907
ciprofloxacin	Cetraxal	yes	-0.157	2.248	1.615	yes	No	0.485	1.013
delafloxacin	Baxdela	yes	0.746	2.142	2	yes	No	0.285	1.997
levofloxacin	Levaquin	No	0.425	2.218	1.802	yes	No	0.285	1.332
moxifloxacin	Avelox	No	0.846	2.166	1.6	yes	No	0.285	2.02
gemifloxacin	Factive	No	0.93	2.024	1.786	yes	No	0.285	2.256
clindamycin	Acanya	No	0.901	2.464	3.194	yes	No	0.285	1.97
lincomycin	Lincocin	No	1.259	2.593	3.405	yes	No	0.285	3.463

4. Conclusion

This work focused on the investigation of 60 different antibiotics evaluating their main toxicity parameters through pkCSM database, including Max. Tolerated Dose (Human) (log mg/kg/day), Oral Rat Acute Toxicity (LD50) (mol/kg), Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day), and Minnow Toxicity (LC50) (log mM). From these results four potential antibiotics are showed less toxicity effects which are cefotaxime, ceftriaxone, imipenem, and meropenem respectively. They have demonstrated lower toxicity compared to other compounds. These findings suggest that these antibiotics may have a relatively favorable safety profile when considering these specific toxicity parameters. However, it's crucial to interpret these results in the context of the specific clinical application and to consider additional factors for a comprehensive safety assessment.

It's important to note that the assessment of toxicity is complex, and the determination of what is considered "less toxic" can depend on specific criteria and the context of use. Additionally, individual responses to antibiotics can vary, and the selection of an antibiotic should be based on various factors, including the specific infection being treated, the patient's health, and potential side effects.

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